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10/763,362	01/23/2004	Mark William Bodmer	674525-2008	7568

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EXAMINER	
HUYNH, PHUONG N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,362	BODMER ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,18 and 29-33* is/are pending in the application.

4a) Of the above claim(s) *18,30,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 7, 2009 has been entered.

2. Claims 1-2, 18 and 29-33 are pending.

3. Claims 18, 30, 32 and 33 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-2 and 31, drawn to a conjugate comprising a first sequence and a second sequence, wherein the first sequence comprises an antibody or antibody fragment which binds to an antigen presenting cell (APC), and wherein the second sequence comprises a Notch ligand or a fragment thereof, wherein the second sequence comprises a Notch ligand DSL domain and at least one EGF-like repeat, and wherein the second sequence retains Notch signaling activity that read on the species of the first sequence comprising antibody or antibody fragment that binds to CD206 as the antigen presenting cell surface molecule and the species of second sequence comprising a human Delta1 as the Notch ligand are being acted upon in this Office Action.

5. Claim 1 is objected to for encompassing non-elected embodiments.

6. Claim 29 is objected to because a conjugate is made by chemical conjugation, NOT by transforming of host cell as claimed. Only fusion protein is prepared by transforming a host cell with an expression vector.

7. Rejections withdrawn

8. The rejection of claims 1-2, 8, 29, 31 and 35 under 35 U.S.C. 102(b) as being anticipated by WO 98/20142 publication (of record, published May 14, 1998; PTO 1449) has been obviated by the claims amendment filed July 7, 2009.

9. The new matter rejection of claim 35 under 35 U.S.C. 112, first paragraph, has been obviated by the claims amendment filed July 7, 2009.

10. The rejection of claims 1-2, 8, 29, 31 and 36 under 35 U.S.C. 102(b) as being anticipated by EP 0861894 B1 (newly cited published Sept 2, 1998; PTO 892) has been obviated by the claims amendment filed July 7, 2009.

11. The rejection of claims 1-2, 8, 29, 31 and 36 under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,664,098 B1 (newly cited, filed Dec 30, 1999; PTO 892) has been obviated by the claims amendment filed July 7, 2009.

12. The rejection of claims 1 and 35 under 35 U.S.C. 103(a) as being unpatentable over WO 98/20142 publication (of record, published May 14, 1998; PTO 1449) in view of Snider et al (newly cited, J Immunology 139: 1609-1616, Sept 1987; PTO 892), US 20030148316 application (newly cited, claimed earliest priority to provisional application filed August 1,2001; PTO 892), Wollenberg et al (newly cited, J Invest Dermatol 118: 327-334, 2002; PTO 892), and/or Noorman et al (newly cited, J Leukocyte Biology 61: 63-72, 1997; PTO 892) has been obviated by the claims amendment filed July 7, 2009.

13. The rejection of claims 1 and 36 under 35 U.S.C. 103(a) as being unpatentable over WO 98/20142 publication (of record, published May 14, 1998; PTO 1449) in view of Snider et al (J Immunology 139: 1609-1616, Sept 1987; PTO 892), US 20030148316 application (newly cited, claimed earliest priority to provisional application filed August 1,2001; PTO 892), Wollenberg et al (newly cited, J Invest Dermatol 118: 327-334, 2002; PTO 892), and/or Noorman et al (newly cited, J Leukocyte Biology 61: 63-72, 1997; PTO 892) as applied to claims 1 and 35 and further in view of US Pat No 6,664,098 B1 (newly cited, filed Dec 30, 1999; PTO 892) or US Pat No 6,136,952 (newly cited, Oct 24, 2000; PTO 892) has been obviated by the claims amendment filed July 7, 2009.

14. Rejections remain

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-2, 29 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a conjugate comprising an antibody or antigen binding fragment thereof which binds to an APC surface molecule selected from the group consisting of CD205 (DEC205), CD204, CD 14, CD206, TLR, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54, BDCA-2, BDCA-3, BDCA-4 wherein the antibody or binding fragment thereof is conjugated to a human Notch ligand selected from the group consisting of human Delta1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, a human Notch ligand fragment selected from the group consisting of the amino acid sequence of SEQ ID NO: 25, SEQ ID NO: 29, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38 and SEQ ID NO: 39 wherein the fragment retains Notch signaling activity; (2) a fusion protein comprising an antibody or antigen binding fragment thereof which binds to an APC surface molecule selected from the group consisting of CD205 (DEC205), CD204, CD 14, CD206, TLR, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54, BDCA-2, BDCA-3, BDCA-4 wherein the antibody or binding fragment thereof fused to a human Notch ligand selected from the group consisting of human Delta1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, a human Notch ligand fragment selected from the group consisting of the amino acid sequence of SEQ ID NO: 25, SEQ ID NO: 29, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38 and SEQ ID NO: 39; (3) a composition comprising the conjugate or fusion protein mentioned above and a pharmaceutically acceptable excipient, diluent, or carrier for targeting Notch ligand to antigen presenting cell and (4) a fusion protein prepared by (a) transforming a host cell with an

expression vector comprising a polynucleotide sequence encoding the fusion protein mentioned above and (b) culturing the host cell under conditions which provide for expression of said fusion protein, **does not** reasonably provide enablement for (1) any conjugate or fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any antibody or any antibody fragment comprising any variable region and which binds to any antigen presenting cell (APC) surface molecule such as CD206 and the second sequence comprises *any* fragment of any Notch ligand such as any fragment of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, any fragment of human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, any fragment of human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, any fragment of human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, or any fragment of Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, and wherein the second sequence retains Notch signaling activity, (2) any conjugate prepared by (a) transforming a host cell with an expression vector comprising a polynucleotide sequence encoding any conjugate mentioned above and (3) a composition comprising any conjugate mentioned above and a pharmaceutically acceptable excipient, diluent or carrier for a method for preventing or treating any disease or infection in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claim 1 encompasses any conjugate or fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any antibody or any antibody fragment comprising any variable region and which binds to any antigen presenting cell (APC) surface molecule such as CD206, and the second sequence comprises a Notch ligand or *any* fragment thereof selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41,

human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, and wherein the second sequence comprises any Notch ligand DSL domain and at least one EGF-like repeat and retains Notch signaling activity.

Claim 2 encompasses any fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any antibody or any antibody fragment comprising any variable region and which binds to any antigen presenting cell (APC) surface molecule such as CD206, and the second sequence comprises a Notch ligand or *any* fragment thereof selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, and wherein the second sequence comprises any Notch ligand DSL domain and at least one EGF-like repeat and retains Notch signaling activity.

Claim 29 encompasses any conjugate mentioned above is prepared by (a) transforming a host cell with an expression vector comprising any polynucleotide sequence encoding such *conjugate* and (b) transforming the host cell under conditions which provide for expression of the conjugate.

Claim 31 encompasses a composition comprising any conjugate or fusion protein mentioned above and a pharmaceutically acceptable excipient, diluent, or carrier for preventing or treating any and all diseases or infections.

Enablement is not commensurate with how to make and use any conjugate or fusion protein mentioned above comprising a first sequence and a second sequence wherein the first sequence comprises any antibody or any antibody fragment comprising just any variable region which binds to an antigen presenting cell (APC) surface molecule such as CD206 and the second sequence comprises any Notch ligand selected from the group consisting of SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44 or any *fragment thereof* wherein the second sequence retains any Notch signaling activity for treating any or preventing or treating any disease or infection.

The specification discloses only a conjugate comprising a MHC class II binding domain of superantigen TSST1 consisting of SEQ ID NO: 45 as shown at page 41 or Figure 7 conjugated

to a Notch ligand Jagged 1 as disclosed on page 66-67 wherein the superantigen TSST1 binds to major histocomplex class II antigen expressed on antigen presenting cell (APC) and wherein the Notch ligand binds to Notch. However, none of the conjugate or fusion protein comprising any fragment of human Delta 1, human Delta 3, human Delta 4, human Jagged 1 or human Jagged 2 has been demonstrate fused to or conjugated to an antibody or antibody fragment retains any notch signaling activity in vitro or in vivo.

The specification hypothesizes the use of any conjugate or fusion protein mentioned above is for modulating, i.e., to inhibit or to stimulate any T cell signaling pathways, upregulating expression of any Notch, upregulating any activity of any Notch signaling pathway, upregulating expression of any Notch ligand, upregulating any activity of any Notch ligand or and downstream component of any Notch signaling pathway for treating any diseases (see specification pages 30-34).

However, there is a lack of *in vivo* working examples of any fragment of human Delta 1, human Delta 3, human Delta 4, human Jagged 1 or human Jagged 2 retains any signaling activity in vitro or in vivo, let alone to treat or to prevent all diseases or infection in any subject.

There is no guidance as to which fragment of Notch ligand selected from the group consisting of SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44 retains which signaling activity, in turn, effective to treating any and all disease, let alone for prevention of all diseases. A fragment could be as little as one amino acid. There is no known or disclosed correlation between the structure of fragment and signaling activity.

There are no working example of using any notch ligand fragment when conjugated to or fused to any antibody or fragment thereof still maintains binding to which notch receptor, much less retaining upstream or down stream signaling activity, inhibition or stimulation of antigen presenting cell. Further, the term "comprises" is open-ended. It expands the Notch ligand fragment to include additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added such that the conjugate or fusion protein retains structure and function.

There is a lack of guidance as to which amino acids within the full-length sequence of which Notch ligand to be deleted such that the Notch ligand fragment still maintains its structure and retains which activity when binds to which Notch receptor, in turn, signaling by modulating, i.e. inhibiting or stimulating which T cell signaling pathway. The Notch signaling in T cell function has a tremendous number of both upstream and downstream effector molecules. The

state of the art as summarized by Tsukumo et al (of record, J Immunology 173: 7109-7113, 2004; PTO 892) is such that there are conflicting evidence for Notch signaling on mature T cell activation and differentiation (see abstract, page 7112, in particular). In mammals, there are four Notch receptors (Notch 1-4) and at least five Notch ligands (Jagged 1 and 2, Delta1, 3 and 4) are identified (see page 7109, col. 2, in particular). However, the detailed relationship between Notch signaling and T cells activation/differentiation has not been established (see page 7112, col. 1, in particular). The receptors and ligands can interact with each other and the expression pattern of each molecule is not restricted, which makes it difficult to analyze the role of Notch systems in mature T cell differentiation/activation and how T cells utilize different Notch molecules to regulate their own differentiation. As such, one skilled in the art at the time of the invention would not be able to predict which fragment in any of the notch ligand protein are tolerant to change that will not result in abolishing which signaling activity of the second sequence for the claimed conjugate. One skilled in the art at the time of the invention would not be able to predict which fragment of any notch ligand functions as an agonist while which other fragment functions as an antagonist in the T cell signaling pathway. One skilled in the art at the time of the invention would not be able to predict which fragment of any notch ligand activates which target genes of the Notch signaling pathway.

Even if the notch ligand is the full-length sequence of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SQE ID NO: 43 or Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, there is no showing of any conjugate or fusion protein comprising such Notch ligand sequence to any antibody or binding fragment thereof that binds to APC surface molecule such as CD206 retains any signaling activity in vitro or in vivo, much less for preventing or treating any and all diseases or infections.

With regard to antibody or antibody fragment comprising "*a* variable region" which binds to antigen presenting cell surface molecule such as CD206 for the claimed conjugate which encompassed conjugate as well as fusion protein, neither the prior art nor applicants' disclosure defines the structure of *a* variable domain of any antibody or antibody fragment can still bind specifically to CD206 or any antigen presenting cell surface molecule.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy *and* light chain variable regions of a

given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target antigen or APC surface molecule. The amino acid sequences and conformations of each of the heavy *and* light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS (all six CDRs) in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce an antibody or binding fragment thereof having that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

The specification proposes antibody or binding fragment thereof that binds to an antigen presenting cell surface molecule such as CD206, MHC class II molecule, CD205 (DEC205), CD204 as a targeting moiety. However, there are no teachings of the structure of any variable domain of any antibody or binding fragment thereof for making and using the claimed conjugate. There is no teaching of just one variable region from VL or VH still retained binding activity to CD206.

Barrios et al (J Molecular Recognition 17: 332-338, 2004; PTO 892) teach the amino acid residues in the CDRs and the length of the antibody heavy chain complementarity determining region (CDR3) are critical for antigen specific binding site (see abstract, in particular). The length of the amino acid sequence that linked the CDRs of immunoglobulin light and heavy chains is important in maintaining their required conformation for binding and in vivo activity.

Note, amending claim 1 to recite "…first sequence comprises an antibody or binding fragment thereof which binds to an antigen presenting cell (APC) surface molecule…" would obviate this rejection.

With respect conjugate prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the conjugate (claim 29), in addition to the problem with the first and second sequence in the claimed conjugate or fusion protein mentioned above, the specification discloses only fusion protein is prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the fusion protein, see page 14, lines 24-30.

The specification does not teach any conjugate is made by prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the conjugate as claimed. It is known in the art that fusion protein is made by recombinant process whereas

conjugate is made by chemical crosslinking. Fusion protein and conjugate are made by two very different processes. The prior art does not teach conjugate is made by transforming a host cell with an expression vector comprising a polynucleotide sequence encoding such conjugate. Note, amending claim 29 to dependent from claim 2 would obviate this rejection.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed July 7, 2009 have been fully considered but they are not persuasive.

Applicants' position is that claim 1 has been amended to recite "[a] conjugate comprising a first sequence and a second sequence, wherein: the first sequence comprises an antibody or antibody fragment comprising a variable region and which binds to an antigen presenting cell (APC) surface molecule, wherein the APC surface molecule is selected from the group consisting of an MHC class II molecule, CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD68, CD83, CD33, CD54 and BDCA-2,3,4; and the second sequence comprises a Notch ligand or a fragment thereof, wherein the second sequence comprises a Notch ligand DSL domain and at least one EGF-like repeat, wherein the Notch ligand is selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, and wherein the second sequence retains Notch signaling activity." With this in consideration, Applicants submit that the specification provides substantial guidance for the instant claims. For instance, the components of the claimed conjugate of claim 1 are described on page 3, lines 3-8, while the APC surface molecules recited in claim 1 are discussed on page 12, lines 17-19, and on page 13, lines 5-10. Notably, the specification describes polypeptides which can bind to MHC Class II molecules on page 39, line 18 - page 41, line 24. Further, the Notch ligand recited in claim 1 is disclosed on page 48, line 26 - page 50, line 49 of the specification as originally filed, and on page 38, lines 25-30 in the specification as amended on June 28, 2004. In addition, the working examples demonstrate how to prepare a conjugate comprising N-terminal 90 amino acids of TSST-1 and an N-terminal fragment of human Jagged l. Based on these teachings, one of ordinary skill in the art can prepare the scope of conjugates encompassed by the instant claims.

With respect to fragment of which Notch Ligand retains Notch signaling activity, the instant claim indeed recite the Notch ligands formerly presented in claim 36. Hence, the skilled artisan can arrive at the claimed conjugate.

Applicants additionally submit that the Office Action concedes that the specification is enabling for "(1) a conjugate comprising an antibody or antigen binding fragment thereof which binds to an APC surface molecule selected from the group consisting of CD205 (DEC205), CD204, CD 14, CD206, TLR, Langerin (CD207), DC-SIGN (CD209), CD68, CD83, CD33, CD54, BDCA-2, BDCA-3, BDCA-4 wherein the antibody or binding fragment thereof is conjugated to a human Notch ligand selected from the group consisting of human Delta l comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, a human Notch ligand fragment selected from the group consisting of the amino acid sequence of SEQ ID NO: 25, SEQ ID NO: 29, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38 and SEQ ID NO: 39 wherein the fragment retains Notch signaling activity" (see Office Action, paragraph bridging pages 3 and 4). Applicants point out that instant claim 1 recites antibody and antibody fragments and Notch ligands that the Office Action has deemed enabled.

In response, amended claim still encompass any conjugate or fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any antibody or any antibody fragment comprising any variable region and which binds to any antigen presenting cell (APC) surface molecule such as MHC class II molecule, CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD68, CD83, CD33, CD54 and BDCA-2,3,4; and the second sequence comprises a Notch ligand or *any* fragment thereof, wherein the second sequence comprises a Notch ligand DSL domain and at least one EGF-like repeat, wherein the Notch ligand is selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, and wherein the second sequence retains Notch signaling activity.

Enablement is not commensurate with how to make and use any conjugate or fusion protein mentioned above comprising a first sequence and a second sequence wherein the first sequence comprises any antibody or any antibody fragment comprising just any variable region which binds to an antigen presenting cell (APC) surface molecule such as CD206 and the second sequence comprises any Notch ligand fragment from SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44 wherein the second sequence retains any Notch signaling activity for treating any or preventing or treating any disease or infection.

There is no guidance as to which fragment of Notch ligand selected from the group consisting of SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44 retains which signaling activity, in turn, effective to treating any and all disease, let alone for prevention of all diseases. A fragment could be as little as one amino acid. There is no known or disclosed correlation between the structures of fragment having signaling activity.

There is not a single working example of any notch ligand fragment when conjugated to or fused to any antibody or binding fragment thereof still retains which signaling activity such as activates or inhibits upstream or down stream signaling activity in antigen presenting cell and/or T cell.

Although the specification exemplified a fusion protein comprising N-terminal 90 amino acids of TSST-1 fused to an N-terminal fragment 260 amino acids of human Jagged l of SEQ ID NO: 43, such Jagged 1 fragment is not a representative of any fragment of SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44 having any signaling activity, let alone for preventing or treating any and all diseases or infection using such conjugate or fusion protein.

With regard to antibody or antibody fragment comprising "a variable region" which binds to antigen presenting cell surface molecule such as CD206 for the claimed conjugate which encompassed conjugated as well as fusion protein, neither the prior art nor applicants' disclosure defines the structure of *a* variable domain of any antibody or antibody fragment can still bind specifically to CD206 or any antigen presenting cell surface molecule for the claimed conjugate or fusion protein.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy *and* light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target antigen or APC surface molecule. The amino acid sequences and conformations of each of the heavy *and* light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS (all six CDRs) in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce an antibody or binding fragment thereof having that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

The specification discloses antibody or binding fragment thereof that binds to an antigen presenting cell surface molecule CD206, MHC class II molecule, CD205 (DEC205), CD204 as a targeting moiety that fused to or crosslinked to a notch ligand of SEQ ID NO: 40, 41, 42, 43 or 44 for targeting said notch ligand to the notch receptor expressed on APC.

There are no teachings that just any one variable region from heavy *or* light chain of an antibody or *antibody fragment* can still bind to an antigen presenting cell surface molecule such as CD206, MHC class II molecule, CD205 (DEC205), or CD204 for the claimed conjugate or fusion protein.

Barrios et al (J Molecular Recognition 17: 332-338, 2004; PTO 892) teach the amino acid residues in the CDRs and the length of the antibody heavy chain complementarity determining region (CDR3) are critical for antigen specific binding site (see abstract, in particular). The length of the amino acid sequence that linked the CDRs of immunoglobulin light and heavy chains is important in maintaining their required conformation for binding and in vivo activity.

There is no teaching of identifying which variable domain, i.e., VL or VH antibody regions and still retain binding activity to CD206. Note, amending claim 1 to recite "…first sequence comprises an antibody or binding fragment thereof which binds to an antigen presenting cell (APC) surface molecule…" would obviate this rejection.

With respect to conjugate prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the conjugate (claim 29), in addition to the problem with the first and second sequence in the claimed conjugate or fusion protein mentioned above, the specification discloses only fusion protein is prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the fusion protein, see page 14, lines 24-30. The specification does not teach conjugate is made by prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the conjugate as claimed. It is known in the art that fusion protein is made by recombinant process whereas conjugate is made by chemical crosslinking. Fusion protein and conjugate are made by two very different processes. The prior art does not teach conjugate is made by transforming a host cell with an expression vector comprising a polynucleotide sequence encoding such conjugate.

Thus the structure of such first and second sequences in the claimed conjugate having which signaling activity cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention. Thus the structure of such sequence in the claimed conjugate cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

17. Claims 1-2, 29 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any fragment of any Notch ligand retaining Notch signaling activity linked to or fused to any antibody or antibody fragment comprising just any variable region that binds to any antigen presenting cell surface molecule such as CD206 for the claimed conjugate.

Claim 1 encompasses any conjugate or fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any antibody or any antibody fragment comprising any variable region and which binds to any antigen presenting cell (APC) surface molecule such as CD206, and the second sequence comprises a Notch ligand or *any* fragment thereof selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, and wherein the second sequence comprises any Notch ligand DSL domain and at least one EGF-like repeat and retains Notch signaling activity.

Claim 2 encompasses any fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any antibody or any antibody fragment comprising any variable region and which binds to any antigen presenting cell (APC) surface molecule such as CD206, and the second sequence comprises a Notch ligand or *any* fragment thereof selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, and Jagged 2 comprising the amino acid sequence of SEQ ID

NO: 44, and wherein the second sequence comprises any Notch ligand DSL domain and at least one EGF-like repeat and retains Notch signaling activity.

Claim 29 encompasses any conjugate mentioned above is prepared by (a) transforming a host cell with an expression vector comprising any polynucleotide sequence encoding such *conjugate* and (b) transforming the host cell under conditions which provide for expression of the conjugate.

Claim 31 encompasses a composition comprising any conjugate or fusion protein mentioned above and a pharmaceutically acceptable excipient, diluent, or carrier for preventing or treating any and all diseases or infections.

At the time of filing, applicants are not in possession of any antibody or antibody fragment comprising just any one variable region and still binds to an antigen presenting cell surface molecule and second sequence comprises any Notch ligand fragment from SEQ ID NO: 40, 41, 42, 43, or 44 having or retaining any Notch signaling activity for the claimed conjugate or fusion protein.

The specification as filed does not describe which "fragment" of any of the disclosed Notch Ligand" retains Notch signaling activity. The specification does not teach how to make and use any Notch ligand fragment that retains which Notch ligand signaling transduction activity in T cells. There is a lack of guidance as to which amino acids within the full-length sequence of which Notch ligand to be deleted, added and/or combination thereof such that the Notch ligand still maintains its structure and retains which activity when binds to which Notch receptor, in turn, signaling by modulating, i.e. inhibiting or stimulating which T cell signaling pathway. Further, the term "comprises" is open-ended. It expands the Notch ligand fragment to include additional amino acids at either or both ends. There is a lack of description as to which amino acids to be added and still retain Notch signaling activity. A fragment could be as little as one amino acid. There is a lack of correlation between the structures of fragment having signaling activity.

The Notch signaling in T cell function has a tremendous number of both upstream and downstream effector molecules. The state of the art as summarized by Tsukumo et al (of record, J Immunology 173: 7109-7113, 2004; PTO 892) is such that there are conflicting evidence for Notch signaling on mature T cell activation and differentiation (see abstract, page 7112, in

particular). In mammals, there are four Notch receptors (Notch 1-4) and at least five Notch ligands (Jagged 1 and 2, Delta1, 3 and 4) are identified (see page 7109, col. 2, in particular). However, the detailed relationship between Notch signaling and T cells activation/differentiation has not been established (see page 7112, col. 1, in particular). The receptors and ligands can interact with each and the expression pattern of each molecule is not restricted, which makes it difficult to analyze the role of Notch systems in mature T cell differentiation/activation and how T cells utilize different Notch molecules to regulate their own differentiation. Although the specification describes a single N-terminal 260 fragment of human Jagged 1 (SEQ ID NO: 43) linked to TSS1, no signaling activity has been shown using such fragment in vitro or in vivo.

Although the specification exemplified a fusion protein comprising N-terminal 90 amino acids of TSST-1 fused to an N-terminal fragment 260 amino acids of human Jagged l of SEQ ID NO: 43, such Jagged 1 fragment is not a representative of any fragment of SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44 having any signaling activity, in turn, as a composition for treating or preventing any and all diseases or infections.

With regard to antibody or antibody fragment comprising "a variable region" which binds to antigen presenting cell surface molecule such as CD206 for the claimed conjugate, applicants are not in possession of any antibody or binding fragment thereof comprising just one variable region and still binds specifically to APC surface molecule such as CD206 for the claimed conjugate.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy *and* light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target antigen or APC surface molecule. The amino acid sequences and conformations of each of the heavy *and* light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS (all six CDRs) in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce an antibody or binding fragment thereof having that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Barrios et al (J Molecular Recognition 17: 332-338, 2004; PTO 892) teach the amino acid residues in the CDRs and the length of the antibody heavy chain complementarity determining

region (CDR3) are critical for antigen specific binding site (see abstract, in particular). The length of the amino acid sequence that linked the CDRs of immunoglobulin light and heavy chains is important in maintaining their required conformation for binding and in vivo activity.

The specification proposed antibody or binding fragment thereof that binds to an antigen presenting cell surface molecule such as CD206, MHC class II molecule, CD205 (DEC205), CD204 as a targeting moiety when fused to or crosslinked to a notch ligand of SEQ ID NO: 40, 41, 42, 43 or 44 for targeting said notch ligand to the notch receptor expressed on APC.

However, the specification does not describe the structure of any variable region of any and all antibody or antibody fragment and still retains binding to APC surface molecule such as CD206. Note, amending claim 1 to recite "…first sequence comprises an antibody or binding fragment thereof which binds to an antigen presenting cell (APC) surface molecule…" would obviate this rejection.

With respect to conjugate prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the conjugate (claim 29), in addition to the issues with the first and second sequence in the claimed conjugate or fusion protein mentioned above, the specification discloses only fusion protein is prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the fusion protein, see page 14, lines 24-30.

The specification does not describe conjugate other than fusion protein is made by prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the conjugate as claimed. It is known in the art that fusion protein is made by recombinant process whereas conjugate is made by chemical crosslinking. Fusion protein and conjugate are made by two very different processes. The prior art does not teach conjugate is made by transforming a host cell with an expression vector comprising a polynucleotide sequence encoding such conjugate. As such, the method of preparing conjugate other than fusion protein by transforming a host cell with an expression vector comprising any polynucleotide sequence encoding such conjugate is not adequately described.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

In this case, the specification provides one Notch ligand fragment consisting of N-terminal first 260 amino acids of SEQ ID NO: 43 fused to TSS1 is not a representative of a genus of conjugate or fusion protein comprising any antibody or antibody fragment comprising just any one variable region that binds to APC surface molecule such as CD206 and any second sequence such as any Notch ligand fragment that retains any signaling activity for treating or preventing any disease or infection to meet the written description provision of 35 U.S.C. § 112, first paragraph.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Further, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of conjugate or fusion protein to describe the genus for the claimed conjugate or fusion protein comprising any antibody or antibody fragment which binds to any antigen presenting cell (APC) and any second sequence comprises any Notch ligand or any fragment thereof comprising a Notch ligand DSL domain and one or more EGF-like repeat.

Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 1-2, 29 and 31. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of the Written Description Training materials, posed April 11, 2008 http://www.USPTO.gov/web/menu/written.pdf.

Applicants' arguments filed July 7, 2009 have been fully considered but they are not persuasive.

Applicants' position is that claim 1 has been amended, the instant claims do not encompass any 'first sequence comprising any antibody or any antibody fragment that binds to any APC' and second sequence such as any Notch ligand fragment comprises a DSL domain and one or more EGF-like repeat wherein the second sequence retains Notch signaling activity without the amino acid sequence" (see Office Action,
page 10); rather, the instant claims provide a structure of the claimed conjugate.

Claim 35 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, because the Office Action contended that the specification discloses only superantigen, and not antibody or antibody fragment, as being capable of binding to MHC class II molecule on APC. Applicants note that claim 35 is cancelled, thereby rendering its rejection moot.

However, Applicants note that the specification indicates that proteins that bind to MHC class II molecules, other than superantigens, may be developed or discovered. For example, the specification recites "[i]t will be appreciated that one can apply conventional protein binding assays to identify molecules which bind to APC surface molecules. It will also be appreciated that one can apply structural-based drug design to develop sequences which bind to APC surface molecules" (specification, page 13, lines 18-21). Thus, the specification teaches that proteins that may bind to APC surface molecules such as MHC class II molecules are not restricted to superantigens. Consequently, claim 35 is supported in the specification.

In response, the arguments with respect to canceled claim 35 are moot since said claim is no longer rejected. Although claim 1 has been amended, amended claim 1 and dependent claims thereof encompass any conjugate or fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any antibody or any antibody fragment comprising any variable region and which binds to any antigen presenting cell (APC) surface molecule such as CD206, and the second sequence comprises a Notch ligand or *any* fragment thereof selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, and Jagged 2 comprising the amino acid sequence of SEQ ID

NO: 44, and wherein the second sequence comprises any Notch ligand DSL domain and at least one EGF-like repeat and retains Notch signaling activity.

At the time of filing, applicants are not in possession of any antibody or antibody fragment comprising just any one variable region and still binds to an antigen presenting cell surface molecule and second sequence comprises any Notch ligand fragment from SEQ ID NO: 40, 41, 42, 43, or 44 having or retaining any Notch signaling activity for the claimed conjugate or fusion protein for preventing or treating any and all diseases.

The specification as filed does not describe which "fragment" of any of the disclosed Notch Ligand" retains Notch signaling activity. The specification does not teach how to make and use any Notch ligand fragment that retains which Notch ligand signaling transduction activity in T cells. There is no disclosure as to which amino acids within the full-length sequence of which Notch ligand to be deleted, added and/or combination thereof such that the Notch ligand still maintains its structure and retains which activity when binds to which Notch receptor, in turn, signaling by modulating, i.e. inhibiting or stimulating which T cell signaling pathway, activates or inhibits which genes in APC. Further, the term "comprises" is open-ended. It expands the Notch ligand fragment to include additional amino acids at either or both ends. There is a lack of written description about which amino acids to be added and still retain Notch signaling activity.

The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same or retaining the same signaling activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

With regard to antibody or antibody fragment comprising "a variable region" which binds to antigen presenting cell surface molecule such as CD206 for the claimed conjugate which encompassed conjugated as well as fusion protein, neither the prior art nor applicants' disclosure defines the structure of *a* variable domain of any antibody or antibody fragment can still bind specifically to CD206 or any antigen presenting cell surface molecule for the claimed conjugate or fusion protein.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy *and* light chain variable regions of a

given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target antigen or APC surface molecule. The amino acid sequences and conformations of each of the heavy *and* light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS (all six CDRs) in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce an antibody or binding fragment thereof having that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

The specification discloses antibody or binding fragment thereof that binds to an antigen presenting cell surface molecule CD206, MHC class II molecule, CD205 (DEC205), CD204 as a targeting moiety that fused to or crosslinked to a notch ligand of SEQ ID NO: 40, 41, 42, 43 or 44 for targeting said notch ligand to the notch receptor expressed on APC.

There is no disclosure of just any one variable region from heavy *or* light chain of an antibody or *antibody fragment* can still bind to an antigen presenting cell surface molecule such as CD206 for the claimed conjugate or fusion protein.

Barrios et al (J Molecular Recognition 17: 332-338, 2004; PTO 892) teach the amino acid residues in the CDRs and the length of the antibody heavy chain complementarity determining region (CDR3) are critical for antigen specific binding site (see abstract, in particular). The length of the amino acid sequence that linked the CDRs of immunoglobulin light and heavy chains is important in maintaining their required conformation for binding and in vivo activity.

There is no teaching of identifying which variable domain, i.e., VL or VH antibody regions and still retain binding activity to CD206. Note, amending claim 1 to recite "…first sequence comprises an antibody or binding fragment thereof which binds to an antigen presenting cell (APC) surface molecule…" would obviate this rejection.

With respect to conjugate prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the conjugate (claim 29), in addition to the problem with the first and second sequence in the claimed conjugate or fusion protein mentioned above, the specification discloses only fusion protein is prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the fusion protein, see page 14, lines 24-30. The specification does not describe any conjugate is made by prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding

the conjugate as now claimed. It is known in the art that fusion protein is made by recombinant process whereas conjugate is made by chemical crosslinking. Fusion protein and conjugate are made by two very different processes. Neither the specification nor the prior art teaches a conjugate is made by transforming a host cell with an expression vector comprising a polynucleotide sequence encoding such conjugate as claimed.

Although the specification exemplified one Notch ligand fragment consisting of the N-terminal first 260 amino acids of human Jagged 1 of SEQ ID NO: 43 fused to the N-terminus of TSS1, there is no disclosure such Jagged 1 fragment retains any signaling activity. Further, one species of human jagged 1 fragment is not representative of other Notch ligand fragment having any signaling activity. TSS-1 is not a representative of antibody or antibody fragment comprising any variable region which still binds to any APC surface molecule such as the ones recited in claim 1.

Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of conjugate or fusion protein to describe the genus for the claimed conjugate or fusion protein comprising any antibody or antibody fragment which binds to any antigen presenting cell (APC) surface molecule such as the ones recited in claim 1 and any second sequence comprises any Notch ligand fragment thereof comprising a Notch ligand DSL domain and one or more EGF-like repeat to show that the applicant would have been in possession of the claimed genus as a whole at the time of filing. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims mentioned above.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Further, Possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111,

Friday January 5, 2001 and revision of the Written Description Training materials, posed April 11, 2008 http://www.USPTO.gov/web/menu/written.pdf.

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

19. Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "A *conjugate* prepared by *transforming* a host cell…" in claim 29 is ambiguous and indefinite because transforming host cell produces fusion protein, NOT a conjugate. A conjugate involves chemical coupling of two proteins, see specification at page 26, lines 11-27. The specification at page 24-25 discloses the *fusion polypeptide* or fusion protein is produced by transforming host cell with an expression vector comprising a polynucleotide encoding the fusion polypeptide to produce the fusion protein. It is suggested that claim 29 be depended from claim 2.

Applicants' arguments filed July 7, 2009 have been fully considered but they are not persuasive.

Applicants' position is the according to MPEP § 2111.01 (IV), "applicant is entitled to be his or her own lexicographer." With this in mind, Applicants draw attention to specification as originally filed, page 26, lines 3-10, which recites that "[c]onjugates of the invention can be recovered and purified from recombinant cell cultures by well-known methods... " Hence, the term "conjugate" as used in the specification and the claims encompasses a product of chemical coupling as well as a product of transformation of a host cell. Therefore, instant claims 2 and 29 are not indefinite.

In response, the argument with respect to claim 2 is moot since the rejection of claim 2 has been withdrawn.

However, a conjugate prepared by (a) transforming a host cell with an expression vector comprising a polynucleotide sequence encoding the conjugate of claim 1 which encompassed fusion protein and conjugate of claim 1 is indefinite.

According to MPEP§ 2173.05(a), any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998). See also *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999) and MPEP § 2173.05(a). The specification should also be relied on for more than just explicit lexicography or clear disavowal of claim scope to determine the meaning of a claim term when applicant acts as his or her own lexicographer; the meaning of a particular claim term may be defined by implication, that is, according to the usage of the term in >the< context in the specification. See *Phillips v. AWH Corp.*, *>415 F.3d 1303<, 75 USPQ2d 1321 (Fed. Cir. 2005) (*en banc*); and *Vitronics Corp. v. Conceptronic Inc.*, 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996). Compare *Merck & Co., Inc., v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1370, 73 USPQ2d 1641, 1646 (Fed. Cir. 2005), where the court held that patentee failed to redefine the ordinary meaning of "about" to mean "exactly" in clear enough terms to justify the counterintuitive definition of "about." ("When a patentee acts as his own lexicographer in redefining the meaning of particular claim terms away from their ordinary meaning, he must clearly express that intent in the written description.").

In this case, the specification discloses only fusion protein, which is prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the fusion protein, see page 14, lines 24-30.

The specification does NOT define a conjugate is prepared by transforming host cell with an expression vector comprising a polynucleotide sequence encoding the conjugate as now claimed.

It is ordinary known in the art that fusion protein is made by recombinant process whereas conjugate is made by chemical crosslinking. Fusion protein and conjugate are made by two very different processes. Neither the specification nor the prior art teaches a conjugate is made by transforming a host cell with an expression vector comprising a polynucleotide sequence encoding such *conjugate*. As such, the claimed term “A conjugate is prepared by transforming a host cell with an expression vector comprising a polynucleotide encoding the conjugate of claim 1 and culturing the host cell under conditions which provide for expression of the conjugate” is indefinite.

Amending claim 29 to be depended from claim 2 would obviate this rejection.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

22. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
August 14, 2009